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TITLE OF PROJECT: Addiction Liabilities of Synthetic Substitutes for Codeine.

Objectives: To find a synthetic analgesic and antitussive drug which would be as safe from the point of view of toxicity and addiction liability as is codeine.

ABSTRACT (OR SUMMARY) OF RESULTS

a. Since start of project:

This portion of the summary of results covers the period from 1 July 1951 to 30 October 1957. The project was undertaken because no synthetic drug was available which was as safe with respect to toxicity and addiction liability as was codeine. Since 75 per cent of the country's needs for narcotic drugs are for codeine, rather than for potent analgesics of the morphine type, the United States must continue to stockpile opium until adequate synthetic substitutes for codeine are developed. The role of the NIMH Addiction Research Center in this investigation, which was begun at the request of the Committee on Drug Addiction and Narcotics of the National Research Council, consists of the determination of addictive properties of the new drugs. The clinical evaluation of the analgesic and antitussive potency of the new drugs must necessarily be made elsewhere.

The methods used for studying the addiction liabilities of new analgesics have been described in detail in the project descriptions in previous reports and will not be repeated here.

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During the period of 1 July 1951 to 31 December 1956, 46 new drugs or mixtures of drugs have been tested for addictive potentialities. Detailed information concerning these substances can be found in the annual reports for 1954 through 1956. Two substances which were outstanding as possible substitutes for codeine for suppression of cough were found. These were: (1) d-3-methoxy-N-methylmorphinan (dextromethorphan), and (2) narcotine. Further clinical reports continue to indicate that dextromethorphan is equivalent to codeine in antitussive potency. It, therefore, seems a very satisfactory codeine substitute for relief of cough. It is already available and on sale in the United States. Narcotine is now on sale and reports of clinical trials of this drug are indicating that it may also be a useful antitussive substitute for codeine.

Since two promising substitutes for codeine for the relief of cough have been developed attention has been turned to finding a compound which would be as effective and as safe as codeine in relieving mild grades of pain. Seven potential substitutes for codeine for pain relief were listed in the report for 1955. In 1955 and 1956 considerable attention was given to the compounds known as dl-propoxyphene and d-propoxyphene. Continuing clinical reports indicate that these drugs are reasonably effective substitutes for codeine in relief of pain. Complete data on toxicity under clinical conditions are, however, not yet available. This drug is now being marketed in the United States by Eli Lilly and Company.

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b. During the current reporting period:

During the current reporting period the addictive potentialities of five drugs were evaluated wholly or in part. The results are presented below under individual headings:

(1) d-1,2-Diphenyl-4-dimethylamino-3-methyl-2-propionoxybutane (d-propoxyphene). Work on this compound was completed and the results reported to the Drug Addiction Committee in January 1956. The results continue to support those previously described. In former addicts the drug does not induce a full spectrum of subjective effects resembling those induced by morphine. It does suppress abstinence from morphine partially, but not completely. When it is administered chronically to nontolerent volunteers some degree of tolerance to the sedative effects is observed. Following withdrawal after chronic intoxication, symptoms of abstinence are milder in degree than those after withdrawal of codeine. It was concluded that d-propoxyphene had definite addiction liability which, however, was far less than that of codeine. The Drug Addiction Committee has therefore recommended that this particular agent not be controlled by the U. S. narcotic laws.

(2) Normorphine. Studies of this agent were undertaken for two reasons: first, it is the precursor of the morphine antagonists which have less addiction liability than does morphine; secondly, it is a normal metabolic product of morphine which is formed by N-demethylation of morphine. As tolerance to morphine is acquired in male rats the ability of the liver to demethylate morphine is reduced. Studies of its addiction liability, therefore, seem to be important theoretically as well as practically. In single doses, normorphine is far less potent than morphine in inducing sedation. In repeated dose, however, it is more potent than morphine. On chronic administration, the dose of normorphine cannot be raised as rapidly or to as high a level as can the dose of morphine. Tolerance to the sedative effects develops more slowly than does tolerance to the sedative effects of morphine. The administration of n-allylnormorphine to persons chronically intoxicated with normorphine precipitates mild symptoms of abstinence. When normorphine is withdrawn after a period of chronic intoxication, symptoms of abstinence are milder than those seen after withdrawal of morphine; they are, in fact, milder than those seen after withdrawal of either codeine or methadone. Despite this the drug suppresses abstinence from morphine completely. It is therefore concluded that normorphine has definite

addictive liability which is probably less than that of codeine. The characteristics of normorphine are such that, if it is an analgesic in man, it should be an excellent drug in conditions associated with chronic pain.

(3) Norcodeine. Studies of norcodeine were undertaken because of the low addictiveness of the parent compound, normorphine. These studies are still incomplete. Preliminary studies indicate that norcodeine will probably have the same relationship to codeine as normorphine has to morphine. In repeated dose, norcodeine is more potent in inducing sedation than is codeine. As is true of normorphine, abstinence is extremely mild following withdrawal of norcodeine after chronic intoxication. The drug is effective orally, so it is a promising substitute for codeine; unfortunately, however, it is not a synthetic.

(4) L-3-Hydroxymorphinan (Norlevorphan). This compound is the analogue of normorphine in the morphinan series. Only preliminary information is as yet available. Single doses ranging up to 70 mg. total do not induce any behavioral changes resembling those seen after morphine or normorphine. In repeated dose, evidence of mild morphine-like effects were observed after administration of 20 mg. four times daily for one day. It does suppress abstinence from morphine completely when given in 50 per cent greater dose than the addicting dose of morphine. At the moment the data are not sufficient to give an estimate of the relative addiction liability of this compound.

(5) d-3-methoxy-N-phenethylmorphinan (NIH-7296A).

We previously reported that this compound partially suppressed abstinence from morphine. This result was entirely unexpected since a congener, d-3-hydroxy-N-phenethylmorphine, was inactive in this respect. Since this result could possibly have been due to contamination with the potent l-form of the drug, especially purified samples of this compound were obtained and tested. The purified drug also partly suppressed abstinence from morphine when given in six times the accustomed dose of morphine. This confirms the previous result and excludes the possibility of the result being due to contamination with the levo-isomer. The addiction liability of the drug is judged to be low, and is probably less than that of codeine.

PLANS FOR FUTURE:

Immediate: During the coming eight months we intend to complete studies on norcodeine and on nordromoran. As soon as possible studies on l-3-methoxy-morphinan, the codeine analogue of nordromoran, will be initiated and compared with the results obtained with codeine and norcodeine. We also intend to restudy the addictiveness of d-methadone. The latter project is being undertaken at the request of the Secretary of the Drug Addiction Committee. Because of the promising results with nor-compounds of morphine and nordromoran we also intend to undertake basic work on the metabolism, excretion, distribution, and fate of some of these drugs in man.

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Long Range: We intend to continue the search for substitutes for codeine until drugs are found which are, in the opinion of the Committee on Drug Addiction and Narcotics of the National Research Council, completely satisfactory substitutes for codeine.

REPORTS AND PUBLICATIONS (during current report period).

1. Fraser, H. F., and Isbell, H.: Further studies on d-1,2-Diphenyl-4-Dimethylamino-3-Methyl-2-Propionoxybutene (d-Propoxyphene). Addendum Min. 18th Meeting, Comm. on Drug Addiction and Narcotics, National Research Council, Indianapolis, Ind. 21-23 January 1957.

2. Fraser, H. F., and Isbell, H.: Addiction Liability of New Analgesics:

i. 1-(2-morpholinethyl)-4-phenyl-4-carbethoxy-piperidine (NIH-7289).

ii. 1-(2-Hydroxy-2-phenethyl)-4-phenyl-4-carbethoxy-piperidine (NIH-7292).

iii. l-3-Methoxy-N-phenethylmorphinan (NIH-7362).

iv. d-2,2-Diphenyl-3-Methyl-4-Morpholino-butyryl-pyrrolidine (NIH-7422).

Addendum Min. 18th Meeting, Comm. on Drug Addiction and Narcotics, National Research Council, Indianapolis, Ind. 21-23 January 1957.

3. Fraser, H. F., Isbell, H., and Van Horn, G. D.: Effects of Morphine as Compared with a Mixture of Morphine plus Diamino-Phenyl-Thiazole (Daptazole). Anesthesiology, 18: 531 (July-Aug.) 1957.

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